

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/635 // (A61K 31/635, 31:495)</b>	<b>A1</b>	(11) International Publication Number: <b>WO 97/24128</b> (43) International Publication Date: 10 July 1997 (10.07.97)
(21) International Application Number: <b>PCT/US96/19946</b> (22) International Filing Date: 10 December 1996 (10.12.96) (30) Priority Data: 08/579,461 27 December 1995 (27.12.95) <b>US</b> (71) Applicant: <b>BAYER CORPORATION [US/US]; One Mellon Center, 500 Grant Street, Pittsburgh, PA 15219 (US).</b> (72) Inventors: <b>GROH, Michael; 612 S.W. Third Street, Lee's Summit, MO 64063 (US). MCCURDY, Dennis; 9910 Ballentine, Overland Park, KS 66214 (US). CABRERA, Francisco, A.; 9953 Marty, Overland Park, KS 66212 (US).</b> (74) Agent: <b>AKORLI, Godfried, R.; Bayer Corporation, 100 Bayer Road, Pittsburgh, PA 15205 (US).</b>	(81) Designated States: <b>AU, BB, BG, BR, BY, CN, CZ, HU, IL, JP, KR, KZ, LK, NO, NZ, PL, RO, RU, SK, TR, UA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: <b>OTIC MICROBIAL COMBINATIONS</b> (57) Abstract <p>Disclosed herein is an otic composition that is useful in treating otic infections comprising an antimicrobial such as a quinolone or a salt thereof and silver sulfadiazine in a therapeutically effective combination to treat otic infections in animals.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## OTIC MICROBIAL COMBINATIONS

### BACKGROUND OF THE INVENTION

#### Field of Invention:

The present invention relates to otic formulations and antimicrobial agents and more specifically to otic formulations containing a combination of antimicrobials such as quinolones and silver sulfadiazine.

#### 5 Brief Description of the Prior Art:

U.S. Patent 4,404,197 discloses the use of certain quinolones and silver sulfadiazine in treating burns. More specifically, the patent discloses compositions that include silver sulfadiazine and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolone carboxylic acid or  
10 its metal salts, e.g., silver, zinc, cobalt or cerium salts. Distinctly, the patent teaches the use of these compositions in treating burns, and in combating topical, surface or skin infections, including microbial and fungal infections and the like. However, the patent fails to teach or suggest the use of the compositions for otic applications.

15 U.S. Patent 3,761,590 discloses the use of silver sulfadiazine alone in burn therapy. Silver sulfadiazine, preferably in a water-dispersible hydrophilic carrier, is applied to the burn.

Bogaard et al, Dep. Med. Microbiol., Univ. Limburg, Netherlands discloses the use of silver sulfadiazine cream in treating chronic  
20 *Pseudomonas* infection of the external auditory canal in dogs.

As would be realized, there is a need for an effective composition for treating otic infections. The present invention provides a therapeutically effective combination of active ingredients that are useful in treating otic infections.

#### 25 SUMMARY OF THE INVENTION

In accordance with the foregoing, the present invention encompasses a composition that is useful in treating otic infections in

- 2 -

animals, said composition comprising a therapeutically effective combination of an antimicrobial such as an antibacterial agent which preferably a quinolone or a salt thereof, and silver sulfadiazine. The invention further encompasses the use of a composition comprising a therapeutically effective combination of an antimicrobial such as an antibacterial agent which is preferably a quinolone or a salt thereof, and silver sulfadiazine in treating otic infections.

Also, encompassed by the present invention is a process for treating otic infections by administering the composition to animals, particularly, small animals such as dogs. The composition containing a combination of an antimicrobial such as an antibacterial agent which is preferably a quinolone and silver sulfadiazine can be administered as such or with a physiologically acceptable carrier such as an oil in water emulsion.

The composition can be used to safely and efficaciously treat otic infections such as infections of the outer ear canal. In particular, the composition can be used to treat infections caused by the bacteria *Pseudomonas*, or fungus, *Malessezia pachydermitis*. The invention is described more fully hereunder.

#### DETAILED DESCRIPTION OF THE INVENTION

As set forth above, the present invention relates to a composition that is useful in treating otic infections. The composition comprises a therapeutically effective combination of an antimicrobial such an antibacterial agent which is preferably a quinolone or a salt thereof and silver sulfadiazine. Typically, the quinolone is a fluorinated quinolone. The effective combination is described hereunder with specificity as to quinolones. The invention, however, encompasses combinations of silver sulfadiazine and other antimicrobial which can combined with the silver sulfadiazine to provide effective treatment of otic infections in the manner of the combination of silver sulfadiazine and quinolones.

- 3 -

Non-limiting examples of the fluorinated quinolone can be selected from the group consisting of Enrofloxacin; 6-Fluoro-1,4-dihydro-1-(methylamino)-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Amifloxacin); Benofloxacin; 6-Fluoro-1-(4-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Difloxacin); 5 Flerofloxacin; 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Fleroxacin); 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Lomefloxacin); Marbofloxacin; 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)-3-quinolonecarboxylic acid (Norfloxacin); 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (Ofloxacin); Perfloxacin; Rufloxacin; Sarafloxacin; and Temafloxacin. The fluorinated quinolone preferred herein is Enrofloxacin. U.S. Patent 4,556,658 which is incorporated 15 herein by reference provides an illustrative but non-limiting description of the quinolone with particularity to Enrofloxacin and a method of preparing the same.

The quinolone or the salt thereof and the silver sulfadiazine are employed in an amount sufficient to provide a composition that would be 20 pharmaceutically effective. The quinolone or the salt thereof can be employed in an amount of 0.005 to 1.5 percent by weight of the composition and preferably 0.1 to 1 percent by weight of the composition. Silver sulfadiazine can be employed in an amount of 0.05 to 2 percent of the composition, and preferably in an amount of 0.5 to 1.5 percent of the 25 composition.

In the preparation of the composition, the quinolone and silver sulfadiazine can be combined in any convenient manner. For example, comminuted silver sulfadiazine and the quinolone can be mixed with each other. The composition can be used directly or preferably in formulation 30 with a pharmaceutically acceptable physiological carrier.

- 4 -

A non-limiting example of a pharmaceutically acceptable physiological carrier can be an oil in water emulsion. Typically, the oil is a non-irritating emollient oil. An illustrative but non-limiting example thereof can be selected from the group consisting of a mineral oil, vegetable oil and a reformed vegetable oil of known composition. More specific but non-limiting examples of the oil can be selected from the group consisting of peanut oil, sesame seed oil, cottonseed oil, etc.; a medium chain ( $C_6$  to  $C_{12}$ ) triglycerides (e.g., Miglyol Neutral Oils 810, 812, 818, 829, 840, etc.) available from Huls America Inc. Typical emulsifiers employed herein can be selected from the group consisting of Span 60 which is sorbitan monostearate and Tween 60, which is Polysorbate 60 (both of which are available from ICI Americas). Preferably, the emulsifiers are nonionic. The emulsifiers can be employed in an amount of 1.5 to 6.5 percent by weight of the composition and preferably 3.0 to 5.0 percent by weight of the composition. The hydrophobic phase of the emulsion can be in an amount of 15.0 to 25.0 percent by weight of the composition and preferably 18.0 to 22.0 percent by weight of the composition.

It is a distinct feature of the invention that the composition of the invention can be formulated as an emulsion base comprising oil in water emulsions described herein. Heretofore, silver sulfadiazine had been formulated as a cream base or a solid synthetic dressing for use in burn therapy. Related silver nitrate solutions were considered undesirable.

In addition to the above components, a formulation of the composition of the invention may contain other components such as preservatives (benzyl alcohol, parabens, or benzoates), stabilizers (cetyl stearyl alcohol, glycerol esters), odor masking agents, and coloring agents.

The following is an illustrative but non-limiting description of a method of providing the compositions of the invention. In a properly

- 5 -

equipped vessel, an emulsifier and a fatty acid alcohol are heated in an oil to form a suspension, and the active ingredients are added to the suspension. In a different vessel, an emulsifier is added to hot water to form an aqueous solution. To the solution are added a preservative and  
5 the suspension with vigorous mixing. The resulting mixture comprising the composition of this invention is effective in treating otic infections.

In treating an otic infection, the composition is preferably administered by applying it topically in a pharmaceutically effective amount. The composition can be applied at a dose of five to twenty  
10 drops per ear and preferably at a dose of eight to twelve drops per ear as needed to coat the ear canal. The composition can be applied twice a day.

This and other aspects of the invention are further illustrated by the following non-limiting examples in which all parts and percentages  
15 are by weight unless otherwise specified.

#### EXAMPLES

The following examples illustrate the otic compositions of the present invention and methods of preparing and using the same. In the present embodiment of the invention, the silver sulfadiazine and the  
20 quinolone are combined as follows.

Polysorbate 60 (Tween 60) was added to water in an SS jacketed tub at a temperature of 50 to 60°C. The resulting aqueous solution was heated to 61 to 75°C. At a temperature of 66°C, a preservative (benzyl alcohol) was added to the aqueous solution while mixing three to ten  
25 minutes.

At a temperature of 75°C Enrofloxacin and silver sulfadiazine were added to Mygliol Oil in a separate vessel over a period of three to five minutes. Sorbitan Monostearate (Span 60) and cetyl stearyl alcohol were added to the oil mixture. The resulting oil mixture was heated to 62 to  
30 75°C. The oil mixture was then added with vigorous mixing to the

- 6 -

- aqueous solution at a temperature of 66°C over a period of three to five minutes. The resulting composition was cooled to 35 to 45°C and homogenized by mixing with a high shear emulsifier or running through a homogenizer. The composition was further cooled to 25 to 30°C. The
- 5 final composition was packaged in appropriate containers.

Examples 1-3 describe the use of the above method and the following ingredients in the parts by weight listed below to prepare formulations containing the compositions of the invention.

Example 1:

10	<u>Ingredients</u>	<u>Parts By Weight</u>
	Enrofloxacin	0.005-1.5
	Silver sulfadiazine(SSD)	0.05-2.0
	Polysorbate 60	0.5-3.5
	Sorbitan monostearate	0.5-3.0
15	Cetyl stearyl alcohol	0.5-3.0
	Benzyl alcohol	1.0-3.0
	Miglyol Oil	8-18
	Water	89.4-68

Example 2:

20	<u>Ingredients</u>	<u>Parts By Weight</u>
	Enrofloxacin	0.5-1.0
	Silver sulfadiazine(SSD)	0.5-1.5
	Polysorbate 60	1.0-3.0
	Sorbitan monostearate	1.0-2.0
25	Cetyl stearyl alcohol	1.0-2.0
	Benzyl alcohol	1.5-2.5
	Miglyol Oil	12-16
	Water	85-74



- 7 -

Example 3:

<u>Ingredients</u>	<u>Parts By Weight</u>
Enrofloxacin	0.5
Silver sulfadiazine(SSD)	1.0
5 Polysorbate 60	2.5
Sorbitan monostearate	1.5
Cetyl stearyl alcohol	1.5
Benzyl alcohol	2.0
Miglyol Oil	14.5
10 Water	76.5

Example 4.

An in vitro microbiology study of the combination of the Enrofloxacin (quinolone) and sulfadiazine was conducted on multiple canine otic pathogens. The study was conducted under the National Committee for Clinical Laboratory Standards (NCCLS) guidelines employing ATCC control organisms for each agar plate tested. Initially, minimum inhibitory concentrations (MICs) were established for each active ingredient. Both enrofloxacin and silver sulfadiazine (SSD) were active on common dermal (otic) pathogens, based on MICs. Each has a different mode of action, though both are bactericidal. The different modes of action reduce the potential for resistance development. Additionally, Enrofloxacin was not effective on *Malassezia* or *Candida* at the concentrations tested. Silver sulfadiazine was effective on both. Evidence of *Malassezia* activity by silver sulfadiazine has not been reported previously.

Using MIC data, there were prepared agar plates containing serial dilutions of each antimicrobial in combination, using a standard checkerboard system. To identify possible interactions between the Enrofloxacin and the silver sulfadiazine, dilutions were prepared, that

- 8 -

were for the most part, from three dilutions above to three dilutions below the MIC for each of the antimicrobials. The patterns of growth (inhibition) of the individual isolates, following exposure to the antimicrobials, were compared. Those of a single genera with the same response were grouped together. All isolates were then subjected to a mathematical calculation designed to indicate whether the antimicrobials were antagonistic, synergistic, or somewhere between. The standard calculation called a Fractional Inhibitory Concentration (FIC) Index is presented below

$$\frac{X}{MIC_x} + \frac{Y}{MIC_y} = FIC_x + FIC_y = FIC \text{ index}$$

- 10 wherein X is equal to a concentration of drug X which is the lowest inhibitory concentration in its row of the checkerboard, and Y is equal to a concentration in its row of the checkerboard. FIC index equal to or less than 0.5 indicates synergism. FIC index equal to or greater than 2.0 indicates antagonism.
- 15 FIC index equal to or greater than 0.5 but less than 2.0 indicates no effect.

For the purpose of comparison, the Enrofloxacin was also combined with clotrimazole. Clotrimazole has antifungal activity but essentially no activity on bacteria. The same series of pathogens were used to evaluate both antimicrobial combinations. FIC data from the study indicating response observed for the two combinations are presented below. (Table 1).

- 9 -

**TABLE 1**  
**Antimicrobial Range of Interaction**

		Fractional Inhibitory Concentration Index	
Organism		Enro* + SSD	Enro + Clotr
5	<i>Pseudomonas aeruginosa</i> (15)**	0.507 to 0.75	1.167 to 2.67
	<i>Staphylococcus intermedius</i> (12)	1.5	1.5
	<i>Escherichia coli</i> (7)	0.36 to 1.5	0.8 to 1.8
	<i>Klebsiella pneumoniae</i> (5)	0.62 to 1.5	1.8 to 2.3
	<i>Beta-hemol Streptococcus</i> (9)	0.625 to 1.5	0.75 to 2.25
10	<i>Malassezia sp</i> (12)	1.5	0.56 to 1.5
	<i>Candida sp</i> (4)	1.5 to 1.75	1.5

\*Drug abbreviations are:

Enro = Enrofloxacin

SSD = Silver Sulfadiazine

Clotr = Clotrimazole

15 \*\*Numbers in parenthesis indicates numbers of isolates tested.

As to the isolates reported above, the combination of the Enrofloxacin and silver sulfadiazine had no values in the antagonistic category. The FIC indices for many of the bacterial isolates were less than 1.0 showing a clear tendency towards additive effect. A few  
20 calculations showed synergism. There was less of a tendency to an additive effect with *Malassezia* and *Candida*.

The additive effect of the Enrofloxacin and the silver sulfadiazine could not have been predicted because the combination of antimicrobials with different modes of activity could have just as easily demonstrated  
25 antagonism. Antagonism was clearly demonstrated, for example, with the combination of Enrofloxacin and Clotrimazole. In three of the five bacterial genera reported above, a score of greater than 2 was calculated. Clotrimazole does not have antibacterial activity, yet the data

- 10 -

indicated that the drug apparently interfered with the antibacterial effect of the Enrofloxacin.

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such  
5 detail is solely for that purpose and that variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention except as it may be limited by the claims.

- 11 -

**WHAT IS CLAIMED IS:**

1. A composition that is useful in treating otic infections comprising an antimicrobial and silver sulfadiazine in a therapeutically effective combination to treat otic infections in animals.
- 5 2. The composition of Claim 1 wherein the antimicrobial is a quinolone or a salt thereof.
3. The composition of Claim 2 wherein the quinolone is a fluorinated quinolone, an ester of fluorinated quinolone or a salt of a fluorinated quinolone.
- 10 4. The composition of Claim 3 wherein the fluorinated quinolone is selected from the group consisting of Amifloxacin, Benofloxacin, Difloxacin, Enrofloxacin, Flerofloxacin, Fleroxacin, Lomefloxacin, Marbofloxacin, Norfloxacin, Ofloxacin, Perfloxacin, Rufloxacin, Sarafloxacin, and Temafloxacin
- 15 5. The composition of Claim 4 wherein the fluorinated quinolone is Enrofloxacin.
6. The composition of Claim 1 wherein the antimicrobial is present in an amount of 0.005 to 1.5 percent by weight of the composition.
- 20 7. The composition of Claim 6 wherein the antimicrobial is present in an amount of 0.1 to 1 percent by weight of the composition.
8. The composition of Claim 1 wherein the sulfadiazine is present in an amount of 0.05 to 2 percent of the composition.
9. The composition of Claim 8 wherein the sulfadiazine is  
25 present in an amount of 0.5 to 1.5 percent of the composition.
10. The composition of Claim 1 which further comprises a physiologically acceptable carrier.
11. The composition of Claim 10 wherein the carrier comprises an emulsion.

- 12 -

12. The composition of Claim 11 wherein the emulsion is oil in water.
13. The composition of Claim 11 wherein the emulsion contains an emulsifier that is present in an amount of 1.5 to 6.5 percent by weight of the composition.
14. The composition of Claim 11 wherein the emulsion contains a non-aqueous phase in an amount of 15 to 25 percent by weight of the composition.
15. A method of treating an otic infection in an animal comprising administering the composition of Claim 1 to the animal having the otic infection.
16. The method of Claim 15 wherein the composition is administered in a pharmaceutically effective amount.
17. The method of Claim 15 wherein the composition is administered on a twice daily basis.

# INTERNATIONAL SEARCH REPORT

International Application No

PL./US 96/19946

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/635 //(A61K31/635,31:495)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 404 197 A (FOX JR CHARLES L ET AL) 13 September 1983 cited in the application	1-4,6-14
Y	see the whole document	5,15-17
X	WO 85 01208 A (RESEARCH CORP) 28 March 1985	1-4,6-14
Y	see the whole document	5,15-17
X	US 5 374 432 A (FOX JR DECEASED CHARLES L ET AL) 20 December 1994	1-4,6-12
Y	see the whole document	5,15-17
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

17 April 1997

Date of mailing of the international search report

06.05.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Hoff, P

# INTERNATIONAL SEARCH REPORT

International Application No  
PL./US 96/19946

C4(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J BURN CARE REHABIL, JUL-AUG 1988, 9 (4) P359-63, UNITED STATES, XP000670922 MODAK SM ET AL: "Combined topical use of silver sulfadiazine and antibiotics as a possible solution to bacterial resistance in burn wounds."	1-4, 10-12
Y	see the whole document	5,15-17
Y	--- VET. CLIN. NORTH AM. SMALL ANIM. PRACT., 1994, 24/5 (921-952), USA, XP000670927 ROSYCHUK R.A.W.: "Management of otitis externa" see page 932 - page 940	5,15-17
Y	--- TIJDSCHR DIERGENEESKD, MAR 15 1982, 107 (6) P224-8, NETHERLANDS, XP000671011 VAN DEN BOGAARD AE ET AL: "[Silver sulphadiazine cream in the treatment of chronic Pseudomonas infection of the external auditory canal in fifteen dogs (author's transl)]" see the whole document	15-17
Y	--- DER PRAKTISCHE TIERARZ, vol. 67, no. 11, 1986, pages 963-966, XP000671012 A.E.J.M. VAN DEN BOGAARD ET AL.: "SILBERSULFADIAZINCREME ALS THERPIE BEI CHRONISCHEN PSEUDOMONASINFEKTIONEN DES AUSSEREN GEHÖRGANGES DES HUNDES" see the whole document	15-17
Y	--- J ANTIMICROB CHEMOTHER, SEP 1990, 26 (3) P303-5, ENGLAND, XP000670914 ELIES W: "Local chemotherapy of selected bacterial infections of the ear." see the whole document	15-17
X	--- J. TRAUMA, 1985, 25/1 (27-31), USA, XP000670884 MODAK S. ET AL: "Synergistic action of silver sulfadiazine and sodium piperacillin on resistant Pseudomonas aeruginosa in vitro and in experimental burn wound infections" see the whole document	1,8-12
A	--- EP 0 337 328 A (DAIICHI SEIYAKU CO) 18 October 1989 see the whole document	1-17



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 19946

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 15-17  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No  
PL./US 96/19946

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4404197 A	13-09-83	NONE	
WO 8501208 A	28-03-85	EP 0154622 A	18-09-85
US 5374432 A	20-12-94	NONE	
EP 0337328 A	18-10-89	JP 1258620 A	16-10-89
		AT 109350 T	15-08-94
		AU 3256789 A	12-10-89
		CA 1330946 A	26-07-94
		DE 68917186 D	08-09-94
		DE 68917186 T	05-01-95
		HK 196596 A	01-11-96
		HU 9500407 A	28-09-95
		IE 65859 B	29-11-95
		JP 2573351 B	22-01-97
		JP 3034925 A	14-02-91
		US 5401741 A	28-03-95